REMARKS

Formal Matters

Claims 1-13, 18-23, 27, and 31-62 are pending after entry of the amendments set forth herein.

Claims 1-13, 18-23, 27, and 31-62 were examined. Claims 1-13, 18-23, 27, and 31-62 were rejected. No claims were allowed.

Claims 22 and 27 have been amended to correct the antecedent basis of claim elements.

No new matter has been added.

Withdrawal of Rejections and Objections

The Applicants express gratitude in the Examiner's indication that rejections and objections not reiterated from the previous Office Action have been withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 22 and 27 have been rejected under 35 U.S.C. § 112, second paragraph. The Office Action asserts that claims 22 and 27 are indefinite because certain elements lack antecedent basis. In view of the amendments to the claims, this rejection may be withdrawn.

Rejection Under 35 U.S.C. §112, first paragraph (Written Description)

The Office Action has maintained the rejection of Claims 1-13, 18-23, 27, and 31-62 under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description for the claimed genus of nucleic acid fragments and mutants. In view of the remarks made below, this rejection may be withdrawn.

In maintaining the rejection, the Office Action asserts that "the specification fails to provide a representative number of species for the claimed genus to show that

applicant was in possession of the claimed genus" (Office Action, page 3). In addition, the Office Action also states language with respect to a sequence identity of at least 70%, 75%, 80% or 85% to SEQ ID NO:12 provide only a "partial structure and a skilled artisan would not be able to envision the detailed chemical structure of the genus of proteins encompassed" (Office Action, page 3).

In addition, in response to the Applicants remarks, the Office Action asserts that "information as to where in the claimed sequence changes will occur, if the modification results in contiguous/sequential run of resides, what regions are conserved or the composition of amino acids in the resulting sequence" (Office Action, page 16).

As noted in the response filed on September 17, 2006, the specification provides **at least ten different variants** of SEQ ID NO:12, including E5, E8, E5up, E5down, E57, AG4, AG45, FP6(E57)-NA, E5-NA, and E83. The sequences of the variants are further described at, for example, Figure 16 and page 47, line 35 to page 53, line 20.

In addition, other examples of chromo- or fluorogenic proteins having at least a sequence identity of at least 70% with SEQ ID NO:12 are also provided in the specification, such as, for example, SEQ ID NO:14, SEQ NO:28, SEQ NO:42, SEQ NO:6, and SEQ NO:8. As such these other chromo- or fluorogenic proteins having at least a sequence identity of at least 70% with SEQ ID NO:12 should also be considered as working examples of the of the invention as presently claimed.

Moreover, with respect to conserved regions and locations susceptible to amino acid changes, the Applicants provide herewith Exhibit A. Exhibit A provides an alignment of various chromo- or fluorescent proteins from non-bioluminescent *Cnidarian* species, including those disclosed in the present application (e.g., SEQ ID NOs: 6, 8, 12, 14, 28, 420) as well as two representative fluorescent proteins (mrFP1 and mCherry) from Shaner et al. (Nature Biotechnology, published online November 21, 2004; doi:10.1038/nbt1037 m) (provided with the response filed on January 13, 2006).

Stretches of conserved amino acids within the various chromo- or fluorescent proteins from non-bioluminescent *Cnidarian* species are identified in Exhibit A with an asterisk (individual residues) or a box (conserved stretches of amino acids). With information provided in the application, i.e., SEQ ID NOs: 6, 8, 12, 14, 28, 420, one of skill in the art would be able to prepare an alignment of the sequences and determine that the fluorescent proteins are susceptible to a significant amount of change while still retaining their fluorescent property. Exhibit A establishes that while certain locations within the sequence of the chromo- or fluorescent proteins are conserved, these conserved sequences are not clustered in any one specific location or region of the protein. In fact, as exemplified in Exhibit A, the conserved amino acids as well amino acids susceptible to change are distributed throughout the sequence of the proteins. However, based on the information provided in the application, one of skill in the art would be able to determine the optimal location of the residues of the proteins to target while maintaining the chromo- or fluorescent property.

In view of the above, it is submitted that the claims do comply with the written description requirement. The specification provides multiple representative examples, including working examples of representative nucleic acids encoding exemplary variant proteins, such that one of skill in the art would have no doubt that the applicant was in possession of the invention as claimed at the time the application was filed. Therefore, this rejection may be withdrawn.

Rejection Under 35 U.S.C. §112, first paragraph (Enablement)

The Office Action has maintained the rejection of Claims 1-13, 18-23, 27, and 31-62 under 35 U.S.C. § 112, first paragraph, for allegedly failing to provide enablement for the claimed invention. In view of the remarks made below, this rejection may be withdrawn.

As noted above, the claims are directed to nucleic acids encoding a protein that has an amino acid sequence that is at least 70% identical to the sequence of SEQ ID NO:12.

The Applicants respectfully submit that the quantity of experimentation required to practice the subject invention is reasonable. The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[1]

The Federal Circuit has found that even extensive experimentation is not undue in the molecular biology arts, particularly with respect to polypeptide variants. For example, the court concluded that extensive screening experiments to determine whether a polypeptide variant maintained a biological activity, while being voluminous, were not undue in view of the art which routinely performs such long experiments. The Federal Circuit stated:

> The claimed compositions recite isolated **polypeptides with 60% or more sequence identity to SEQ ID NO:3** that suppress proliferation of lympho-hematopoietic cells. **The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which sequences retain the ability to suppress proliferation of lympho-hematopoietic cells**. The sequence of polypeptides retaining biological activity is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide made by routine recombinant DNA techniques. **Since these experiments are empirical in nature, no undue experimentation is required.** In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since **this only requires a routine assay on polypeptide variants** to determine the active variants, **no undue experimentation is necessary**.[2]

(emphasis added).

The claims of present application are directed to nucleic acids encoding a chromo- or fluorescent protein from a non-bioluminescent Cnidarian species, where the protein has an amino acid sequence that is at least 70% identical to SEQ ID NO:12.

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[1]. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

As in Hybritech, polypeptides according to the invention that retain the chromo- or fluorescent properties are "determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide...Since these experiments are empirical in nature, no undue experimentation is required."[3] In particular, the polypeptides according to the invention that retain the chromo- or fluorescent property can be routinely determined as described in the specification at, for example, page 54, line 32 through page 55, line 34.

Moreover, the Applicants note that the specification provides guidance for the subject nucleic acids at, for example, on page 8, line 11 through page 17, line 6; proteins encoded by nucleic acids are described at, for example, on page 9, line 12 though page 12, line 15; and representative number of species within the claimed genus at, for example, in Table 10 on pages 56-57

Furthermore, Exhibit A also provides guidance with respect to conserved amino acids as well amino acids susceptible to change distributed throughout the sequence of the proteins.

Accordingly, the experimentation is not excessive, voluminous, or undue. Applicants respectfully submit that the specification provides ample guidance and direction, coupled with the information available in the relevant art, for one of skill to practice the claimed invention without undue and excessive experimentation. Therefore, in view of the amendments to the claims, this rejection may be withdrawn.

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[2] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)
[3] *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

CONCLUSION

In view of the above remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone Bret Field at 650 327 3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

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Enclosures:

- Exhibit A – Alignment of Chromo- of Fluorescent Proteins

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